Inorganic Chemistry Communications 54 (2015) 21–24

Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Crystal structures and biological activities of a symmetrical quinoline thioether ligand and its transition metal complexes

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ARTICLE INFO

Article history:
Received 8 January 2015
Received in revised form 24 January 2015
Accepted 28 January 2015
Available online 30 January 2015

Keywords:
2,6-Bis (8-quinolinylthiomethyl) pyridine
Transition metal complexes
Antibacterial activities
Pesticide activities

ABSTRACT

The ligand 2,6-bis (8-quinolinylthiomethyl) pyridine and its four transition metal complexes have been synthesized and characterized by elemental analysis (EA), infrared spectra (IR) and single-crystal diffraction. It was revealed that compounds **1**–**3** were comprised of discrete mononuclear units and double nuclear structure in compound **4**. The antibacterial activities and pesticide activities of the ligand and complexes **1**–**4** were tested. The results showed that some compounds had absolute specificity for certain bacteria, and could have good application prospect in pharmaceutical and agricultural use.

Chemical structure of the compounds containing quinoline thioether group has been the focus of attention. Because of the particularity of the structures, this kind of compounds have a good coordination performance which we can find in Chen and Su's works [1–5], and their fluorescence activity [6] and adsorptive property [7] have been reported before. Recently, this kind of compounds are widely researched in the field of molecular biology, such as ubiquitin agent inhibitors [8], 11-beta-hydroxysteroid dehydrogenase type I inhibitor [9], JAMM protein inhibitor [10], potential 5-HT_6 receptor [11], $CRTh_2$ antagonists [12], and Keap1–Nrf2 Small-Molecule Inhibitors [13]. However, reports on the bioactivities of such kinds of complexes still remain rare. The asymmetric thioether ligand, prepared by Akerkar A. S. in the 1970s, has been proven to be an excellent antitubercular agent [14]. In order to probe the potential drug activity of such kind of compounds, the pyridine terminal group was taken as a carrier, which might be a synergistic activity group we have probed before [15–18], and reacted with 2 times of equivalent of quinoline thiol groups, the symmetry of quinoline sulfur ether ligand 2,6-bis (8-quinolinylthiomethyl) pyridine (L) was synthesized. The complexes of $[Cu(L)(CF_3SO_3)]\cdot(CF_3SO_3)$ (**1**), $[Cd(L)](ClO_4)_2(H_2O)_2$ (**2**), $[Zn(L)(CO_2CF_3)]\cdot(ClO_4)\cdot CH_3CN$ (**3**), and $[Co(L)CoCl_4]\cdot CH_3OH$ (**4**) were obtained by coordinating with a series of transition metal salts. All the compounds were characterized by elemental analysis (EA), infrared spectra (IR) and single-crystal diffraction, their antibacterial and pesticide activities were tested.

Single-crystal X-ray diffraction measurements of the ligand and complexes **1**–**4** were carried out on an Oxford Gemini S Ultra CCD diffractometer equipped with a graphite monochromator at 150 K. The determination of unit cell parameters and data collections were performed with Mo–K_α radiation ($\lambda = 0.71073$ Å). The unit cell parameters were obtained with least-square refinements and all structures were solved by direct methods [19]. The metal atoms in each complex were located from *E*-maps. The other non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was performed by full matrix least-square methods with anisotropic thermal parameters for non-hydrogen atoms against F_0^2 [20]. Hydrogen atoms were added in calculated positions. The O atoms on coordinated CO_2CF_3 and uncoordinated ClO_4 anions are disordered and treated over two positions.

Single-crystal diffraction reveals that the π–π accumulation effect of the two quinoline rings (spacing of 3.359 Å) in 2,6-bis (8-quinolinylmethylthio) pyridine (**L**) forms a one-dimensional chain structure (Fig. S1). The major bond length and bond angle of **L** were listed (Table S1). The crystallographic data and structure refinement summary

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http://dx.doi.org/10.1016/j.inoche.2015.01.029

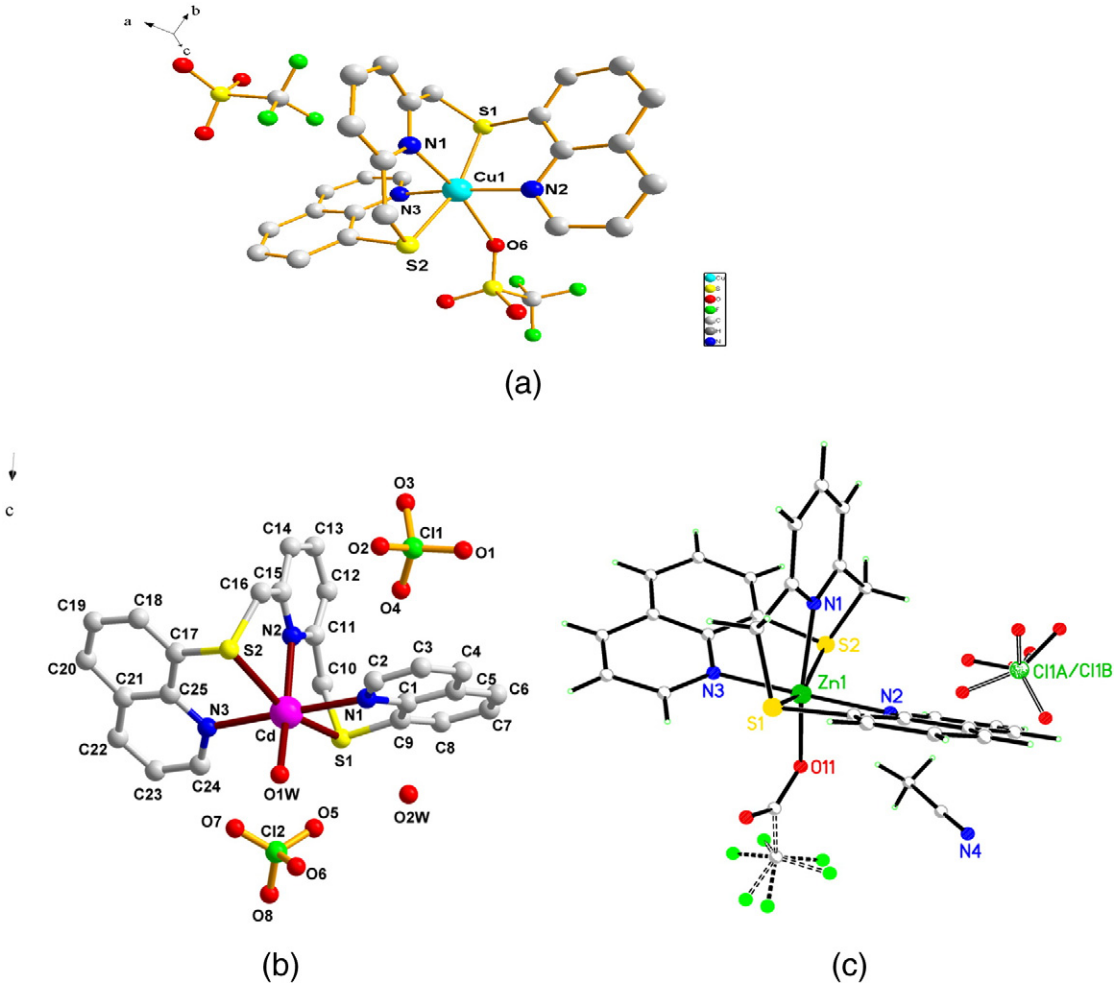

Fig. 1. (**a**) View of the coordination environment of Cu(II) ions in **1**. (**b**) View of the coordination environment of Ni(II) ions in **2**. (**c**) View of the coordination environment of Zn(II) ions in **3**.

data for the ligand and its complexes **1**–**4** are listed in Table S2. The synthesis abstract of the ligand **L** and the complexes **1**–**4** are listed in Fig. S2.

In the complex $[Cu(L)(CF_3SO_3)](CF_3SO_3)$ (**1**), copper ions are six coordinated by nitrogen atoms on the two quinoline rings [Cu–N(2) = 2.000(3) Å, Cu–N(3) = 1.986(3) Å], two sulfur atoms connected with methylene [Cu–S(1) = 2.3837(15) Å, Cu–S(2) = 2.3986(15) Å], nitrogen atoms on the pyridine ring [Cu–N(1) = 2.259(3) Å] and an oxygen atom on the trifluoroacetic acid [Cu–O(1) = 2.555(3) Å], to form a single-core structure. In the asymmetric unit of complex **1**, there is a free trifluoroacetic acid anion which is not participating in coordination (Fig. 1a).

The unit structures of complexes **2** and **3** are basically the same ML coordination model as complex **1**. In the asymmetric unit $[Cd(L)](ClO_4)_2(H_2O)_2$ of complex **2**, the Cd^{2+} is located in the center of

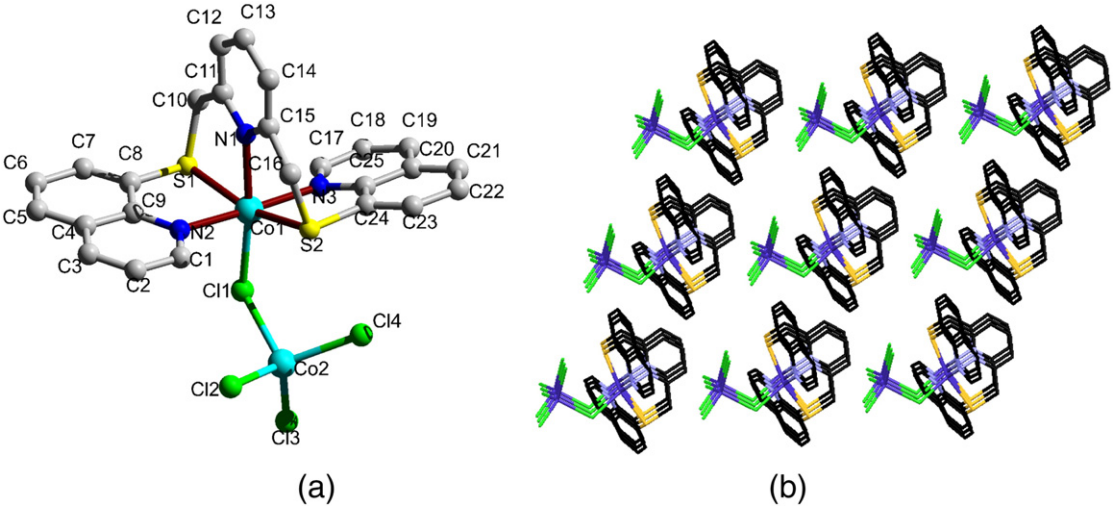

Fig. 2. (a) View of the coordination environment of Co(II) ions in **4**. (b) Molecular accumulation figure of **4**.

Table 1
Tests of MIC (μg/mL) of the ligand and complexes against bacterial and fungal strains.[a]

Compounds	Bacterial			
	S. ureae (G^+)	*P. aeruginosa* (G^-)	*E. coli ATCC 25922* (G^-)	*S. aureus ATCC 27154* (G^+)
Amp[b]	3.13	3.13	6.25	12.5
Str[b]	3.13	1.56	3.13	1.56
L	>50	>50	3.13	>50
1	3.13	6.25	6.25	12.5
2	1.56	3.13	25	0.125
3	>50	>50	50	>50
4	6.25	6.25	12.5	3.13

[a] Results are expressed as the minimum inhibitory concentration (MIC).
[b] Ampicillin (Amp), streptomycin sulfate (Str).

a very slightly distorted octahedral geometry and coordinated by quinoline N and S atoms from the L ligand [Cd–N(1) = 2.288(3) Å, Cd–N(3) = 2.318(3) Å, Cd–S(1) = 2.644(1)Å, Cd–S(2) = 2.655 (1) Å, Cd–N(3) = 2.385(3) Å] and one oxygen atom on water molecule [Cd–O = 2.255(3) Å] (Fig. 1**b**). The asymmetric unit of complex **3** is comprised of one Zn^{2+}, one L, one coordinated CO_2CF_3 anion, one uncoordinated ClO_4 anion and a CH_3CN molecule [Zn(1)–N(1) = 2.254(1) Å, Zn(1)–N(3) = 2.129(1) Å, Zn(1)–S(1) = 2.523(4) Å, Zn(1)–S(2) = 2.518(5) Å, Zn(1)–N(2) = 2.132(1) Å] (Fig. 1c).

Different from the complexes introduced above, the asymmetric unit of $[Co(L)CoCl_4]\cdot CH_3OH$ (complex **4**) is composed of two nuclear cobalt atoms, one ligand and a methanol molecule, forming an M_2L coordination model. Co1 is coordinated with two nitrogen atoms on quinoline rings [Co(1)–N(2) = 2.126(4) Å, Co(1)–N(3) = 2.138(4) Å], two sulfur atoms connected with methylene [Co(1)–S(1) = 2.5036(11) Å, Co(1)–S(2) = 2.4779(11) Å], a nitrogen atom on pyridine ring [Co(1)–N(1) = 2.185(4) Å], and a chloride anion [Co(1)–Cl(1) = 2.4505(12) Å], while Co2 was linked with four chloride anions, forming a double-core structure. The four bond angles between Co2 ion and the chloride anions, Cl(2)–Co(2)–Cl(4) = 115.84(6)°, Cl(2)–Co(2)–Cl(3) = 115.22(6)°, Cl(4)–Co(2)–Cl(3) = 111.27(5)°, reveal that the Co2 ion is coordinated in tetrahedral configuration. The two Co atoms are linked up by Cl bridge. In complex **4**, the bond angles N(2)–Co(1)–N(3) = 176.78(16)°, N(2)–Co(1)–N(1) = 88.20(14)°, N(3)–Co(1)–N(1) = 88.71(14)°, N(2)–Co(1)–Cl(1) = 89.75(11)°, N(3)–Co(1)–Cl(1) = 93.43(11)°, and N(1)–Co(1)–Cl(1) = 171.34(10)° indicate that the pyridine and quinoline rings are almost vertical (Fig. 2).

Because compounds **1**–**4** were comprised of discrete mononuclear units or double nuclear structure and stable in solution, all the complexes were dissolved in DMSO (dimethylsulfoxide) and tested against five aerobic reference strains for their inhibitory activity. The antimicrobial activities were performed using a modified version of the 2-fold serial dilution method as RA Fromtling (1993), in which two starting yeast inoculums' sizes ($5 \times 10(4)$ and $2.5 \times 10(3)$ cells per mL) were compared, and reading were taken after 24 and 48 h of incubation. The resultant turbidities in all tubes were estimated visually on a scale from 0 to ++++ turbidity, and MIC-0, MIC-1 and MIC-2 were defined as the lowest drug concentrations that reduced the growth to 0, + or ++ turbidity, respectively [21]. From the antibacterial results listed in Table 1, we can see that 2,6-bis (8-quinolinylmethylthio) pyridine (**L**) has absolute specificity in *Escherichia coli*, and the MIC was 3.13 μg/mL, which has a similar antibacterial effect with the reference substances of ampicillin and streptomycin and even better; however, poor effect on several other test bacteria. After the ligand was coordinated with Cu^{2+}, Cd^{2+}, and Co^{2+} metals, the antibacterial properties of all the organometallic compounds show declining results for *E. coli*, while the characteristics of broad spectrum antimicrobial activities in complexes **1**, **2** and **4** were presented. The growth of a variety of bacteria can be inhibited effectively, and the minimum bacteriostatic concentration is close to the control group. What merits our primary concern is the fact that complex **2** has a serious strong effect on all the test bacteria, especially the gram-positive bacteria. However, compound **3** with Zn^{2+} metal centers have poor antimicrobial inhibition activity compared with other compounds. Compared with the data published before [18], for example, the MIC of complex $[Cu(L)(CF_3CO_2)]\cdot(CF_3CO_2)\cdot(H_2O)_2$ was 3.13 μg/mL, and $[Zn_2(L)_2(H_2O)_2](ClO_4)_4\cdot(H_2O)_2\cdot(CH_3CN)_2$ was 12.5 μg/mL for *Staphylococcus aureus* under the same test conditions with complexes **1** and **3**, the difference reveals that sulfur ether metal complexes containing pyridine and quinoline groups can have different bactericidal exhibition activities relating to both metal category and the change of molecular space conformational.

The pesticide activities of the complexes except **2** were tested. It can be seen from the data in Table 2 that the ligand and its complexes have a worse pesticide bactericidal activity on *Fusarium oxysporum f. cucumerinum*, showing only 20–50% of the bacteriostatic effect. But the effect of the compounds on *Alternaria solani* and *Physalospora piricola* is outstanding, for example, the antifungal effect of complexes **1** and **3** can reach about to 80%.

In conclusion, the ligand and its four transition metal complexes have been prepared and characterized. The complexes **1**–**4** are either discrete mononuclear (complexes **1**–**3**) or binuclear structure (complex **4**). The antibacterial activity tests show that the ligand has absolute specificity in *E. coli*, and the MIC was 3.13 μg/mL, while all the complexes, except compound **3** with Zn^{2+} metal center, present characteristics of broad spectrum antimicrobial effect. The antibacterial effectiveness of compound **3** is about 2–100 times in the control group for the gram-positive bacteria. In pesticide bactericidal activities, all the complexes show a moderate effect on *Colletotrichum lagenarium and Cercospora rachidicola*. However, complexes **1** and **3** reveal a good bacteriostatic effect on *Alternaria solani* and *P. piricola*, which can reach to about 80%. The research on a detailed reaction mechanism of the ligand and its complexes against bacteria and fungi, may be DNA-binding properties we infer, is proceeding.

Acknowledgment

The authors gratefully acknowledge the Guangdong Province Universities' and Colleges' High Level Talent Project (2011QY01), the Science and Technology Planning Project of Guangdong Province (2012A020603023), the National Natural Science Foundation of China (21373276), the Natural Science Foundation of Guangdong Industry Technical College (KJ201301), and the Construction Technological of Guangdong Province Think Tank Research Subject (2014GDSXK011) for financial support.

Table 2
Pesticide bactericidal activity screening test levels of the complexes.[a]

Compounds	Inhibition ratio/%	Levels [c]	Inhibition ratio/%	Levels [c]	Inhibition ratio/%	Levels [c]	Inhibition ratio/%	Levels [c]	Inhibition ratio/%	Levels [c]
	C [b]		F[b]		U [b]		I [b]		D[b]	
L	20.00	−	50.00	+	5.88	−	26.58	−	68.00	+
1	49.09	−	72.22	++	58.82	+	87.34	++	60.00	+
3	27.27	−	72.22	++	41.18	−	62.03	+	44.00	−
4	20.00	−	44.44	−	64.71	+	21.52	−	68.00	+

[a] Pesticide bactericidal activity is revealed by the percentage of complexes against bacterial.
[b] *Fusarium oxysporum f. cucumerinum* (C), *Alternaria solani* (F), *Colletotrichum lagenarium* (U), *Physalospora piricola* (I), *Cercospora rachidicola* (D).
[c] Activity levels: +++ ≥ 90%; ++ ≥ 70–89%; + ≥ 50–69%; − < 50%.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.inoche.2015.01.029. These data include MOL files and InChiKeys of the most important compounds described in this article.

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